Heart WATCH

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Texas Heart® Institute

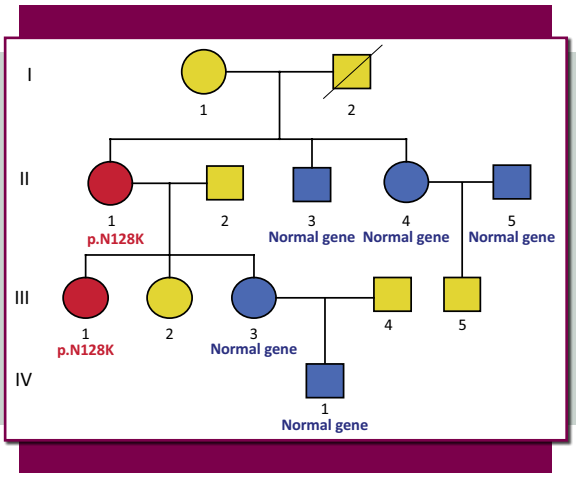
at St. Luke's Episcopal Hospital

Researchers Identify Muscle-Restricted Coiled-Coil (*MURC*) as a Potential Causal Gene for Dilated Cardiomyopathy

Abstract: Genetic variants in *MURC* cosegregate with the inheritance of dilated cardiomyopathy and cause a loss of function in cardiomyocytes.

Dilated cardiomyopathy (DCM) is a form of systolic heart failure for which several causal genes have been identified, including genes that encode sarcomere and cytoskeletal proteins. However, these genes account for only a small percentage of DCM cases, so a significant number of causal genes remain to be identified.

Ali J. Marian, MD, and his colleagues recently identified *MURC* (muscle-restricted coiled-coil) as a potential causal gene of DCM in humans (*Circ Cardiovasc Genet* 2011;4:349-58). Dr. Marian is a member of the Adult Cardiology staff at the Texas Heart Institute at St. Luke's Episcopal Hospital (THI at St. Luke's). He is also the George and Mary Josephine Hamman Foundation Distinguished Professor in Cardiovascular Research at The Brown Foundation Institute of Molecular Medicine at The University of Texas Health Science Center at Houston.



Family studies are crucial for establishing that a genetic variant is a disease-causing mutation. Here, 2 family members are diagnosed with dilated cardiomyopathy (DCM; red) and carry the *MURC* variant p.N128K, whereas 5 family members are clinically normal (blue) and do not carry the variant. Cosegregation of the *MURC* variant with DCM increases the likelihood that the variant is a disease-causing mutation. (Yellow denotes individuals who were not studied; circles and squares denote female and male individuals, respectively; and diagonal lines denote death.) Reprinted from *Circ Cardiovasc Genet* 2011;4:349-58, with permission.

Dr. Marian and his researchers previously discovered that *MURC* regulates cardiac function in mice. The *MURC* gene encodes a cardiac-specific protein found in Z-lines, which mark the actin junction between adjacent sarcomeres. To identify variants in *MURC* that may cause cardiomyopathy, these researchers sequenced the coding regions and splice junctions of the *MURC* gene in a population of individuals with DCM (n=383), hypertrophic cardiomyopathy (HCM; n=307), or no cardiomyopathy (n=509). (Recruitment of the study population was in part supported by the TexGen program at THI at St. Luke's.)

"In 8 individuals with DCM, we identified 6 variants in the *MURC* gene that were not seen in HCM and control individuals. These genetic variants encode single amino acid substitutions in the MURC protein, which may or may not affect the function of MURC in cells," states Dr. Marian. "To get an idea of whether these amino acid substitutions may affect MURC function, we used a predictive software program and found that 4 of the 6 amino acid changes caused by the variants were predicted to be possibly or probably damaging."

To determine whether the program's predictions were accurate, these researchers performed biochemical experiments to characterize the activities of the MURC-mutant proteins in vitro. Under normal conditions, MURC activates the RhoA/Rho-kinase (ROCK) signaling pathway that mediates myofibrillar organization and muscle protein homeostasis, but when overexpressed, MURC causes cardiac hypertrophy. RhoA activity and the expression of cardiac markers of hypertrophy were significantly lower in cardiomyocytes expressing mutant MURC proteins than in cardiomyocytes expressing wild-type MURC ($P<0.05$). Furthermore, the cell surface area was significantly smaller in cardiomyocytes expressing MURC mutants than in cardiomyocytes expressing wild-type MURC ($P<0.05$), indicating that the *MURC* variants impart a loss of function consistent with the computer predictions and the characteristics of DCM.

"In defining a true causal relationship, it is crucial to examine the inheritance pattern of the variants," says Dr. Marian. Thus, the researchers extended their genetic analysis to the family members of the 8 DCM individuals with *MURC* variants. Two of the variants, p.N128K and p.S307T, cosegregated with the inheritance of DCM ($\chi^2=8.5$; $P=0.003$), strongly supporting a causal role for *MURC* in DCM. However, the linkage analyses were limited by small family size and incomplete penetrance.

"Although other possibilities cannot be ruled out, our genetic and functional data strongly favor the causal role of *MURC* variants in the pathogenesis of human cardiomyopathy," concludes Dr. Marian. "Elucidating the genetic causes of heart failure is an essential step toward the ultimate cure of this prevalent and potentially deadly disease." ●

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Texas Heart Institute Surgeons Implant 4 SynCardia Total Artificial Hearts in 12 Days

Abstract: During a recent 12-day period, Texas Heart Institute surgeons implanted the temporary SynCardia Total Artificial Heart in 4 patients with end-stage biventricular failure.

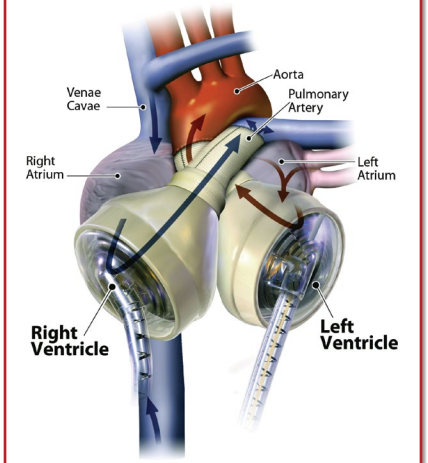
In 2004, after a 10-year clinical study, the US Food and Drug Administration (FDA) approved the SynCardia temporary Total Artificial Heart (TAH) (SynCardia Systems, Inc., Tucson, AZ) as a bridge to transplantation for patients with end-stage biventricular failure. From July 21 through August 1, 2011, surgeons at the Texas Heart Institute at St. Luke's Episcopal Hospital (THI at St. Luke's) implanted the SynCardia device in 4 such patients, bringing the total number of these devices implanted worldwide to more than 950.

To date, cardiac transplantation is the only effective therapy for patients with irreversible biventricular failure. However, the demand for donor hearts greatly outpaces the supply.

The 4 SynCardia TAHs were implanted by a surgical team headed by Igor D. Gregoric, MD, who is Director of the Center for Cardiac Support and Associate Director of Cardiovascular Surgery and Transplant Research at THI at St. Luke's. "Heart transplantation is an effective method of treating terminal heart failure," says Dr. Gregoric. "But it is limited by the scarcity of suitable donor hearts and by the inapplicability of transplantation to patients whose disease has shortened their life expectancy such that they would probably not survive the transplant waiting period. For these patients, who are out of other options, devices such as the SynCardia are absolutely critical."

The SynCardia TAH is a biventricular, pneumatic, pulsatile pump that replaces the native ventricles and all 4 cardiac valves. The pump is lined with polyurethane, and its 4-layer, pneumatically driven diaphragm provides a maximal cardiac output of 9.5 L/min.

For patients in the United States, the SynCardia is powered by a pneumatic driver located in a non-portable console, so the patient must remain in the hospital. However, a new, wearable driver system allowing patients to be discharged home has been approved for use in Europe. SynCardia is currently conducting an FDA-approved Investigational Device Exemption clinical study of the portable driver in the United States.



Drawing of a Syncardia Total Artificial Heart as it would be implanted in a patient. *Courtesy: syncardia.com*.

Among the 4 patients in the present series is a 22-year-old man who, at age 2 years, he had a heart transplant done by O. H. Frazier, MD, Chief of the Center for Cardiac Support at THI at St. Luke's. As a medical student, Dr. Frazier worked on research for the pump used by Drs. Denton Cooley and Domingo Liotta in the first clinical artificial heart implant, in 1969. He later helped develop many other cardiac pumps, including the SynCardia TAH.

"Sometimes patients with biventricular failure need an immediate intervention. They don't have the luxury of waiting," says Dr. Frazier. "The decades we've spent working on this device are now buying these patients the precious time they need."

In most cases, the SynCardia TAH restores blood flow and improves end-organ function, making patients better transplant candidates. In addition, because this pump orthotopically replaces both native cardiac ventricles and all 4 cardiac valves, it eliminates the problems commonly seen when patients are bridged to transplantation with left ventricular or biventricular assist devices; these problems include right-sided heart failure, valvular regurgitation, arrhythmias, clots, and low blood flow. And, according to Dr. Gregoric, patients have a marked improvement in their activity level and their quality of life in general.

"The use of this device as a bridge to transplantation helps restore hemodynamic function and promote end-organ recovery and mobility in these critically ill patients with biventricular failure," says Dr. Gregoric. "For patients whose condition continues to deteriorate despite maximal inotropic support, the SynCardia TAH can provide clinical stabilization and even keep them alive until a donor heart can be found. With this device, a considerable number of potential cardiac transplant recipients with no other options may now have the opportunity to undergo cardiac transplantation." ●

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Contents

Cell Therapy With Aldehyde Dehydrogenase Bright Cells May Benefit Patients With Critical Limb Ischemia

Abstract: The direct intramuscular injection of autologous aldehyde dehyrdogenase bright cells is safe and may be beneficial in patients with critical limb ischemia.

Critical limb ischemia (CLI) involves severe blockage in the arteries of the lower extremities that results in ischemic pain at rest and tissue loss. The reduction in blood flow caused by CLI can be severe enough to threaten the viability of the affected limb. Despite advances in percutaneous and surgical revascularization techniques, almost half of CLI patients are not candidates for revascularization, and 30% to 50% of these patients will undergo amputation.

Stem cell therapy with autologous bone marrow mononuclear cells (BMMNCs) has shown promise as a therapeutic option in CLI patients who are ineligble for revascularization. Researchers at the Stem Cell Center (SCC) at the Texas Heart Institute at St. Luke's Episcopal Hospital (THI at St. Luke's) conducted a double-blind, randomized study to examine the use of a selected population of autologous BMMNCs enriched for angiogenic activities in no-option CLI patients (*Catheter Cardiovasc Interv* 2011; epub ahead of print). These selected cells, called aldehyde dehydrogenase bright ($ALDH^{br}$) cells, are isolated from the bone marrow because they express high levels of the enzyme ALDH. Consitituting about 1% of BMMNCs, the $ALDH^{br}$ population contains stem and progenitor cells for the multiple cell types needed for ischemic repair. The study was led by Emerson C. Perin, MD, PhD, Medical Director of the SCC and Director of Clinical Research for Cardiovascular Medicine at THI at St. Luke's.

The study group comprised 21 patients who were randomly assigned to receive direct intramuscular injections of either $ALDH^{br}$ cells (n=11) or autologous BMMNCs (n=10). The primary endpoint was safety, which was assessed by evaluating adverse events that occurred up to 24 weeks after the cell injections. Efficacy was the secondary endpoint and was examined by assessing CLI symptoms and hemodynamic status at 6 and 12 weeks after the cell injections.

"Our results showed that the intramuscular injection of $ALDH^{br}$ cells in the lower extremity of patients with severe CLI is safe," says James T. Willerson, MD, President and Medical Director of THI at St. Luke's and a study investigator. "The procedure was well tolerated, and no significant side effects or serious adverse events were associated with cell therapy."

The investigators evaluated CLI symptoms by using the Rutherford ischemic limb classification system (ranging from 0 [asymptomatic] to 6 [major tissue loss without salvageable tissue]), by assessing rest pain, and by measuring quality of life. Patients treated with $ALDH^{br}$ cells showed substantial improvement in mean Rutherford category (from 4.09±0.30 at baseline to 3.46±1.04 at 12 weeks; P=0.05). Also, significant improvements in quality-of-life measures, as well as nonsignificant decreases in rest pain, were noted in $ALDH^{br}$ cell–treated patients.

The primary measure of hemodynamic status in the study was ankle brachial index (ABI), which is derived from Doppler-obtained arterial pressure measurements taken at the ankle and brachium. The $ALDH^{br}$ group showed significant improvement in ABI over baseline levels at 6 (P=0.02) and 12 weeks (P=0.025) after cell injections. Transcutaneous oximetry and ulcer grade, also measures of hemodynamic status, were not significantly affected by $ALDH^{br}$ cell treatment.

"Our study showed that $ALDH^{br}$ cell treatment of patients with severe CLI was feasible and safe and may potentially have a positive effect on limb perfusion," says Dr. Perin. "Moreover, our study is unique in that we selected cells from the bone marrow on the basis of an intracellular enzyme that serves as a 'stemness' marker for cells of multiple lineages."

"In most cardiovascular cell therapy trials, unfractionated BMMNCs or cells of a specific lineage selected by the presence of a cell surface marker are used, but this shotgun approach may not yield optimal results," continues Dr. Perin. "Our study identifies not only a new cell type but perhaps a new approach to obtaining cells for stem cell studies." ●

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THI's Center for Coronary Artery Anomalies and Its Kinder Outreach Program

Sudden cardiac death (SCD) in a fit, seemingly healthy student athlete is tragic and shocking. To help prevent SCD in the Houston area, the Center for Coronary Artery Anomalies (CCAA) at the Texas Heart Institute (THI) is conducting a research study in which 10,000 middle school students in the Houston area will be voluntarily screened for unrecognized congenital heart abnormalities that might lead to SCD. The investigators aim to determine whether enough of the students have undetected cardiac abnormalities to justify the screening of all student athletes, or even of all students. The research is underwritten by a $5 million donation from The Kinder Foundation, founded by Houston philanthropists Rich and Nancy Kinder. In gratitude for this generous donation, the study is called The Kinder Outreach Program.

The screening consists of a brief history, an electrocardiogram, and magnetic resonance imaging (MRI). With this imaging technology, the investigators can detect hypertrophic cardiomyopathy and coronary artery anomalies, which together cause about 70% of SCDs in the United States. The tests will be done in a mobile imaging unit equipped with an MRI scanner (Philips Healthcare). This unit will go to each school and provide onsite screenings. The study has been approved by an independent institutional review board, and the screening is free of charge but requires written parental consent.

The principal investigator for the study is James T. Willerson, MD, President and Medical Director of the Texas Heart Institute. The Medical dDirector of the CCAA is THI cardiologist Paolo Angelini, MD.

THI Cardiologists and Rice University Bioengineering Students Invent New Automated External Defibrillator Pads

Abstract: New, user-friendly automated external defibrillator pads let responders act more quickly and more effectively than do standard pads.

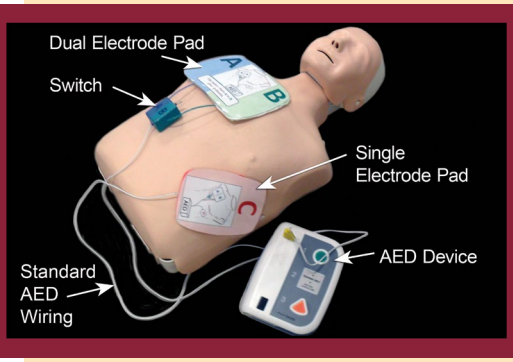
Arrhythmias can cause a cardiac arrest, which can lead to irreversible brain damage and death. For individuals who have an arrhythmic event outside a hospital, swift use of an automated external defibrillator (AED) may be their best hope of survival. Designed to be used by laypersons, AEDs send and receive electrical currents through electrode pads applied to the patient's bare chest. These pads detect electrical output from the patient's heart, and if a shockable rhythm is present, the AED delivers a therapeutic shock.

One option that can be used if the first series of shocks fail is repositioning the pads. With traditional AEDs, the sticky pads must be repositioned on the chest before another current can be sent to the heart, and this can take up valuable time. Moreover, the pads can send currents to the heart only when placed in certain locations. An untrained responder may not know how to reposition the pads or even to reposition them at all.

To address this problem, Mehdi Razavi, MD, a cardiologist and Director of Electrophysiology Clinical Research at the Texas Heart Institute at St. Luke's Episcopal Hospital, and his colleagues collaborated with a team of senior bioengineering students who graduated from Rice University in 2011. This team, dubbed the "Defib TaskForce," consisted of 5 students—Lisa Jiang, Joanna Nathan, Justin Lin, Carl Nelson, and Brad Otto—and their advisor, Renata Ramos, PhD, a lecturer in Rice's bioengineering department.

The collaboration resulted in the invention of a new AED pad system called Second-Chance AED Pads. The provisional patent lists all of the Defib TaskForce members' names along with Dr. Razavi's. With these pads, responders can repeat the defibrillation process without having to reposition the pads on the victim's chest.

"The Second-Chance AED Pads significantly reduce the time between shocks," Dr. Razavi explains. "In using traditional AED pads, responders who need to apply another shock have to remove the pads, prepare a different part of the chest, and reposition the pads before giving the next shock. In using our pads, however, responders just have to flip a switch. This takes much less time, and the system is more likely to administer a shock at the correct location."



An automated external defibrillator (AED) with the Second-Chance AED Pads is used on a medical mannequin.

The system consists of 3 electrodes: 2 in a single pad labeled "A/B" and 1 in a second pad labeled "C." The A/B pad includes an A/B switch. When the AED is first used, it administers 2 shocks from electrode A. If the shocks do not defibrillate the heart, the AED prompts the responder to flip the switch from A to B. This activates electrode B, sending a shock from a new position without the need to reposition the pads.

The team has developed a concise instruction card for use with the Second-Chance AED Pads. To test the final version of the device, the team recruited students with no experience using an AED to shock a medical mannequin's heart into normal activity. All the testers placed the pads correctly. This 100% success rate suggests that the instructions are clear and that the design is intuitive and easy to use. The team hopes that an AED manufacturer will acquire the rights to the Second-Chance AED Pads. Clinical trials would be performed and data submitted to the US Food and Drug Administration for approval.

"Any innovation that enhances a lay person's ability to prevent or reverse cardiac arrest has the potential to save a lot of lives," says Dr. Razavi. "We hope that will be the case with our AED pads." ●

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THI Establishes a Center for Heart Valve Disease

The Texas Heart Institute at St. Luke's Episcopal Hospital (THI at St. Luke's) has established a Center for Heart Valve Disease. The goals of the center are to study and treat valvular heart disease (VHD) and to raise public awareness of the disease. Treatment often involves valve repair or replacement, which typically necessitates open heart surgery. If untreated, VHD can ultimately be fatal.

The Center for Heart Valve Disease focuses on all elements of VHD and its therapy. Treatments under investigation by the center include stem cell therapy and less invasive methods of repairing and replacing valves, which would allow treatment of more VHD patients too sick for open surgical repair.

Researchers believe that the prevalence and cost of treating VHD will increase as "baby boomers" age and the average lifespan becomes longer. Despite the association between increasing age and VHD incidence, people of any age can develop the disease, and VHD is sometimes even congenital.

The Director of the new Center for Heart Valve Disease is Blase A. Carabello, MD, who is also Chief of Medicine at the Michael E. DeBakey Veterans Administration Medical Center. The valve center's Co-Director is R. David Fish, MD, who also leads Interventional Cardiology Research and Education at THI at St. Luke's. Clinicians seeking additional information are encouraged to call 713.791.9400.

Obesity Influences the Incidence of Morbidity But Not Mortality After Coronary Artery Bypass Grafting

Abstract: Compared with non-obese patients, obese patients have a higher incidence of respiratory failure, renal insufficiency, and wound infections but fewer bleeding events after bypass surgery.

Obesity is increasingly prevalent in the United States. Because obesity is associated with a variety of risk factors for coronary atherosclerosis—including diabetes mellitus, hypertension, and hyperlipidemia—obese persons are more likely than normal-weight persons to require a coronary intervention, such as coronary artery bypass grafting (CABG). Obesity is considered by some researchers to be a risk factor for short- and long-term mortality and morbidity after CABG, but the evidence is conflicting. This is particularly true for adverse cardiovascular outcomes; whereas some studies show that obesity is a risk factor for such outcomes, other studies show no relationship or even a protective effect of obesity against these outcomes.

For this reason, James M. Wilson, MD, MacArthur A. Elayda, MD, PhD, and their colleagues at the Texas Heart Institute at St. Luke's Episcopal Hospital (THI at St. Luke's) performed a retrospective cohort analysis of data from 13,115 consecutive patients who underwent isolated CABG procedures at St. Luke's between 1995 and 2010. Dr. Wilson is a cardiologist and Director of Cardiology Education at THI at St. Luke's, and Dr. Elayda is Vice President of Biostatistics and Epidemiology at THI at St. Luke's.

The patients were divided into 2 groups according to their body mass index (BMI): obese patients (BMI $\geq$ 30 kg/m^2) and non-obese patients (BMI < 30 kg/m^2). Then, using propensity-matched stepwise multivariable logistic regression, the investigators examined the independent effects of obesity on an array of outcomes: in-hospital mortality (the primary outcome), length of hospital stay, and the incidences of postoperative respiratory failure, stroke, myocardial infarction, sternal and leg wound infections, atrial fibrillation, ventricular tachycardia, and renal failure. Additionally, to adjust for the possibility that obese patients are generally sicker than non-obese patients, the authors performed the same analyses on propensity-matched subgroups of obese and non-obese patients (n=4221 per group).

> *"Compared with non-obese patients, obese patients tend to have longer operative times and are more likely to have pre-existing diabetes and renal insufficiency. All of these factors may contribute to the elevated rate of sternal wound and leg wound infections in obese patients."*
>
> —James M. Wilson, MD

The results showed no significant relationship between obesity and in-hospital mortality, either in the whole cohort of patients (odds ratio, 0.91; 95% confidence interval, 0.73-1.13) or in the propensity-matched groups (odds ratio, 1.13; 95% confidence interval, 0.86-1.48). However, obese patients were more likely to have postoperative respiratory failure, renal insufficiency, sternal wound infection, and leg wound infection than were non-obese patients. In contrast, obese patients were less likely to have postoperative bleeding or to need reoperation for bleeding.

"We tried using several different cutoff points for BMI to see if any of them resulted in a significant difference in postoperative mortality between obese and non-obese patients," says Dr. Elayda. "None of these cutoff points made a difference, which seems to support the conclusion that obesity itself does not contribute to mortality risk in CABG patients."

"Our findings regarding wound infections were in line with those of previous studies," Dr. Wilson adds. "Compared with non-obese patients, obese patients tend to have longer operative times and are more likely to have pre-existing diabetes and renal insufficiency. All of these factors may contribute to the elevated rate of sternal wound and leg wound infections in obese patients."

The other adverse outcomes significantly associated with obesity—postoperative respiratory failure and postoperative renal insufficiency—have not been found in all studies of obese CABG patients. However, the odds ratios associated with these outcomes were lower than those related to wound infections, so it is possible that some other studies did not have sample sizes large enough to show the effect of obesity on the risk of respiratory failure and renal insufficiency to be statistically significant.

"Our most curious finding," Dr. Wilson says, "was that the obese patients had fewer postoperative bleeding events and reoperations for bleeding than the non-obese patients. It is possible that this outcome results from a procoagulant state that other investigators have associated with metabolic syndrome and obesity. It is also possible that the surgeons who performed the CABG operations used a higher threshold for reoperation for their obese patients than for their nonobese patients. In any case, this is a subject that warrants further study." ●

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CD34+/M-cadherin+ Bone Marrow Progenitor Cells May Protect Against Ischemic Injury in Mice

Abstract: Injection of CD34+/M-cadherin+ bone marrow progenitor cells increases vascularization and blood flow in a mouse model of hindlimb ischemia.

Peripheral arterial disease (PAD) is characterized by insufficient blood flow and ischemia in the lower extremities. Conventional therapies, such as surgical or percutaneous revascularization, result in only partial or short-term correction of ischemia.

One promising alternative is a cell-based approach, wherein autologous bone marrow stem/progenitor cells (BMCs) are injected intramuscularly into ischemic limbs. The BMCs may engraft into ischemic tissues, induce vascular regeneration, and increase blood flow. However, BMC-induced vascularization and reduction of ischemia appear to be limited and short-lived.

Researchers at the Texas Heart Institute at St. Luke's Episcopal Hospital (THI at St. Luke's) and The University of Texas Health Science Center at Houston sought to increase the efficacy of this cell-based approach. "Our goal was to determine whether injecting BMC subpopulations that have maximum angiogenic potential would improve the extent of vascular regeneration induced by this therapy," states Richard A. F. Dixon, PhD, Director of the Wafic Said Molecular Cardiology Research Laboratory at THI at St. Luke's (*PLoS ONE* 2011;6:1-7).

In initial studies, the investigators identified a promising mouse BMC subpopulation for further study; they found that cells that expressed both the CD34 and M-cadherin (M-cad) surface antigens (CD34+/M-cad+ BMCs) localized in vivo to sites of ischemic damage. To characterize these cells, the investigators performed immunophenotyping studies and colony-forming unit assays, both of which suggested that CD34+/M-cad+ BMCs have hematopoietic progenitor cell properties. The researchers then assessed the ability of these BMCs to reduce ischemia in the hindlimbs of hypercholesterolemic ApoE$^{-/-}$ mice.

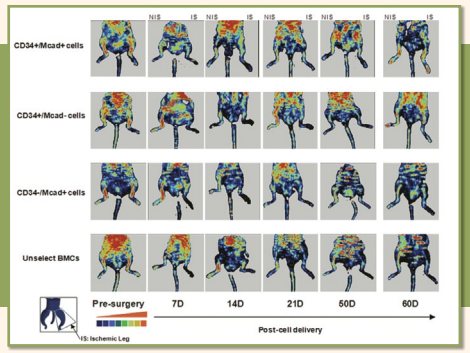
"We used laser Doppler perfusion imaging to examine blood flow recovery in the ischemic hindlimbs of mice treated with CD34+/M-cad+ cells, CD34+/M-cad- cells, CD34-/M-cad+ cells, or unselected BMCs," says Dr. Dixon. "Intra-arterial injection of CD34+/M-cad+ BMCs into the ischemic limb improved blood flow more than the other cell populations for up to 60 days after injection [see Figure]."

The investigators examined the ability of CD34+/M-cad+ BMCs to promote arteriogenesis in hindlimbs. To identify arteries and arterioles, they immunostained tissue sections of ischemic hindlimbs with α-smooth muscle actin (α-SMA) 60 days after cell injection. They found that mice injected with CD34+/M-cad+ BMCs had greater neovascularization in the ischemic hindlimb than mice treated with CD34-/M-cad+ cells ($P<0.01$), CD34+/M-cad- cells ($P<0.001$), or unselected BMCs ($P<0.0001$). To determine whether injected CD34+/M-cad+ BMCs integrated into host tissues, they performed histologic and morphometric analyses of tissue sections at 21 days after injection and found that fluorescently labeled CD34+/M-cad+ cells incorporated into solid tissue structures in the ischemic leg. Moreover, confocal microscopy of ischemic legs treated with fluorescently labeled CD34+/M-cad+ cells, followed by immunostaining of the tissue with vascular cell markers, indicated the vascular differentiation of CD34+/M-cad+ cells.

"We could not, however, find functional arterioles or arteries that originated entirely from CD34+/M-cad+ cells, which suggests that paracrine action, rather than direct vascular differentiation, is primarily responsible for the therapeutic effect of these cells," states Dr. Dixon. "This idea is supported by the results of our cytokine antibody array, which indicated that CD34+/M-cad+ BMCs secrete a unique pattern of proangiogenic cytokines and growth factors."

Using a tube formation assay, the investigators showed that these secreted factors induced endothelial cell sprouting under ischemic conditions in vitro. Their findings suggest that there may be a beneficial interplay among cytokines secreted by CD34+/M-cad+ BMCs that could augment vasculogenic effects in vivo.

"We have identified a novel subpopulation of BMCs that shows hematopoietic proliferative potential and that may promote the growth of arterioles and increase blood flow in ischemic tissue," says Dr. Dixon. "Thus, we believe that CD34+/M-cad+ BMCs may be an excellent candidate for use in the cell-based treatment of PAD." ●



Laser Doppler perfusion imaging indicated that blood flow in ischemic hindlimbs was increased in the CD34+/M-Cad+ BMC-treated group compared with the other treatment groups. IS = ischemic legs, NIS = nonischemic legs. (Reprinted from *PLoS ONE* 2011;6:1-7.)

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Cover: Artwork donated by Nancy Ames & Danny Ward for the Celebration of Hearts display in the Wallace D. Wilson Museum of the Texas Heart Institute at St. Luke's Episcopal Hospital—The Denton A. Cooley Building.

Calendar of Events

Texas Heart Institute Continuing Medical Education Symposia

Future Direction of Stem Cells in Cardiovascular Disease
Satellite Symposium to the American College of Cardiology Scientific Sessions
The Peabody Orlando
November 12, 2011 • Orlando, Florida
Program Director: James T. Willerson, MD

11th Annual Texas Update in Cardiovascular Advancements
Texas Heart Institute
December 10, 2011 • Houston, Texas
Program Director: James T. Willerson, MD

For information about Texas Heart Institute CME activities, please e-mail cme@texasheart.org or call 713-218-2200. To view or complete selected online CME courses (certificates are available online), please visit www.cme.texasheart.org. New courses are added regularly.

Selected Upcoming Local, National, and International Meetings

American College of Surgeons 97th Annual Clinical Congress
October 23–27, 2011 • San Francisco, California
www.facs.org

American Heart Association 2011 Scientific Sessions
November 12–16, 2011 • Orlando, Florida
www.scientificsessions.org

Society of Thoracic Surgeons 48th Annual Meeting
January 28–February 1, 2012 • Fort Lauderdale, Florida
www.sts.org/education-meetings/sts-annual-meeting

International Society for Heart and Lung Transplantation 32nd Annual Meeting and Scientific Sessions
April 18–21, 2012 • Prague, Czech Republic
Abstract submission deadline: November 18, 2011
www.ishlt.org/meetings/annualMeeting.asp

American Association for Thoracic Surgery 92nd Annual Meeting
April 28–May 2, 2012 • San Francisco, California
www.aats.org/annualmeeting/

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For 21 consecutive years, the Texas Heart Institute at St. Luke's Episcopal Hospital has been ranked among the top 10 heart centers in the United States by *U.S. News & World Report*'s annual guide to "America's Best Hospitals."